REMARKS

Claims 1-9, 11, 12, 14, 15, 17-19, 23, 25, and 27-39 were pending in this application. Claims 1-3, 9, 12, 27-29, 31, 33, 34, 37, 38, 40, and 41 are currently amended. Claims 1-9, 11, 12, 14, 15, 17-19, 23, 25, and 27-39 are currently pending. No claims have been canceled.

Support for the amendment to claim 1 may be found in the application as filed at least on page 11, lines 7 and 12 and page 13, line 18. Applicants submit that no new matter has been added.

Withdrawal of Certain Rejections

Applicants thank the Examiner for withdrawing the requirement for a species election, and examining claims 1-9, 11, 12, 14, 15, 17-19, 23, 25, and 27-39.

Objections

The Examiner has objected to the Abstract because it contains legal phraseology that refers to "said peptide." Applicants have submitted a replacement Abstract that replaces this terminology with "the peptide." This correction is believed to address the Examiner's objection.

The Examiner has also objected to claims 1-3, 31, 33, 34, 38, and 40-41 because they either lack appropriate sequence identifiers or they contain sequence identifiers that are improperly formatted. Applicants have amended claims 1-3, 31, 33, 34, 38, and 40-41 to correct these errors or omissions. Applicants have also amended claim 37 to add a sequence identifier for the peptide sequence disclosed therein. Additionally, Applicants have also amended claim 9 to add a sequence identifier for the HIV-TAT_{48-57} peptide. These corrections are believed to address the Examiner's objections.

Applicants respectfully submit that these objections may now be withdrawn.

Rejections under 35 U.S.C. § 112

The Examiner has rejected claims 1-9, 11-12, 14-15, 17-19, 23, 25, and 27-39 under 35 U.S.C. § 112, 1st paragraph, on the grounds that the specification does not enable the full scope of the claims. Specifically, the Examiner has taken issue with the terms "or variants thereof" and "preventing cancer," and also alleged that the specification does not enable the genus of peptides and genotoxins claimed. Applicants respectfully traverse this rejection.

With respect to the two terms, Applicants respectfully disagree with the Examiner's position that the specification does not enable the full scope of the terms "or variants thereof" and "preventing cancer" as used in the claims; however, Applicants have amended the above-cited claims to delete reference to the terms "or variants thereof" and "preventing cancer" for the sole purpose of expediting allowance of the instant application, and not in acquiescence to the Examiner's allegations that these terms are not enabled by the specification. Applicants respectfully submit that this rejection may be withdrawn.

With regard to the alleged lack of written description for the genus of "variants" of the claimed N2 fragment peptides, Applicants respectfully submit that the instant claim amendments render the rejection moot.

Concerning the alleged lack of written description for the genus of "various" genotoxins, Applicants respectfully disagree with the Examiner's position that the "specification does not sufficiently describe the use and effect of peptide variants in enhancing ***various*** genotoxins." As described above, Applicants have deleted the "variant" language with regard to the claimed N2 sequence of the RasGAP protein. In view of this, the instant amended claims are directed, in part, to the combination of a ***specifically defined*** N2 sequence of the RasGAP protein and a genotoxin as particularly claimed in claims 11, 12, 14, 15, and 17-19. Applicants respectfully submit that the predictability of the art with regard to genotoxic agents was extremely high at the time the instant application was filed. Applicants submit that it is well known that these compounds damage DNA and/or prevent cells from multiplying. They all have in common the fact that they are poisonous compounds that damage DNA and thereby induce apoptosis of damaged cells (see, *e.g.*, Roos WP, Kaina B., "DNA damage-induced cell death by apoptosis" in Trends Mol. Med. 12(9), 440-450, 2006). Additionally, Applicants submit that a query of the Pubmed database with the search term "genotoxic agent" identified 2,731 published references

prior to the filing date of the instant application. A further query of these 2,731 references revealed that 503 discussed "alkylating agents," 143 discussed "antimetabolites," 52 discussed "topoisomerase," and 18 discussed "spindle poisons." As a specific example, Applicants note that the state of the art was particularly well developed with regard to the "alkylating agents" elaborated in claim 12. For example, the earliest publication identified in the 503 publications that referenced the term "alkylating agents" pre-dated the instant filing date by three decades (see, *e.g.*, Osterman-Golkar *et al.* (1976) Evaluation of genetic risks of alkylating agents. II. Haemoglobin as a dose monitor. Mutat. Res. 34(1):1-10). Additionally, all of the compounds listed in claim 12 are commercially available from one or more suppliers, and their genotoxic properties are typically listed as part of the product characterization. For example, the Sigma Aldrich catalog describes the alkylating agent mitomycin as an "inhibitor of DNA synthesis, nuclear division, and cancer cells." Moreover, a query of the Sigma Aldrich catalog with the term "genotoxic" identifies 272 products. Applicants respectfully submit that one of skill in the art would understand that Applicants were in full possession of the claimed genus of genotoxins as evidenced by the disclosure that such agents may be selected from the group comprising ***alkylating agents, antimetabolites, DNA cutters, DNA binders, topoisomerase poisons and spindle poisons*** (see *e.g.*, page 9, line 2-26 of the specification) and the presence of ***working examples*** including genotoxins from more than one of these groups, as acknowledged by the Examiner on page 3 and 5 of the Office Action, including ***cisplatin (an alkylating agent) and adriamycin and mitoxantrone (topoisomerase poisons)*** (see, *e.g.*, Examples 1 and 2). In view of the advanced and predictable state of the art pertaining to genotoxic agents, as evidenced by nearly 3,000 references published over a 30 year period and the ready commercial availability of such agents, it is Applicants' position that the disclosure of ***working examples*** incorporating the species ***cisplatin, aadriamycin, and mitoxantrone from multiple groups of known genotoxins*** is more than adequate for one of skill in the art to understand that the Applicants contemplated the use of the full breadth of the claimed genus of genotoxins, and were in full possession of the same at the time the application was filed. In this regard, Applicants submit that genotoxic agents were in such common use at the time the application was filed that one of skill in the art would need very little direction as to what specific genotoxic agents to use in order to build upon and improve the Applicant's invention as presently claimed and disclosed: a central goal of the written description requirement of 35 U.S.C. § 112. Applicants respectfully request favorable reconsideration and withdrawal of this rejection.

Regarding the alleged lack of written description for the specific cancers recited in claims 23 and 25, Applicants respectfully disagree with the Examiner's position. Applicants submit that the application as originally filed fully supports Applicants' position that the pharmaceutical compositions of the invention will solve the technical problem for all of the cancers listed in claims 23 and 25 because the ***working examples*** of the application clearly indicate that fragments of the N2 sequence of the RasGAP protein comprising the general amino acid sequence WxVVVTxxRTx, wherein X represents an amino acid, in combination with a genotoxin, enhances the ability of the genotoxin to selectively kill a ***broad range of cancer cells***, including: ***HeLa cells*** (an immortal cell line derived from a ***malignant cancer of the cervix***); ***MCF7 cells*** (a cellular model of human ***breast cancer***); ***U2OS cells*** (***osteosarcoma*** cells); and ***H-Meso1 cells*** (human ***malignant mesothelioma*** cells). Applicants respectfully submit that these cancer cell lines are representative of the major cancers found in humans, and are routinely used as proxies by those of skill in the art to assess the effect of therapeutic/research agents for application to the specific cancers listed in claims 23 and 25. In view of this, Applicants submit that one of skill in the art would understand that Applicants disclosure of ***working examples*** encompassing ***four different*** cancer cell lines with ***very different cell type specificities*** was more than sufficient to indicate that Applicants contemplated the use of the full breadth of the claimed genus of cancers, and were in full possession of the same at the time the application was filed. For these reasons, Applicants respectfully request that this rejection be withdrawn.

Claims 9, 12, 23, 27, 28, 33-38, and 40-43 are rejected under 35 U.S.C. § 112, 2nd paragraph

The Examiner has rejected claim 9 on the grounds that it is not clear what sequence the recited terms, *e.g.* "HIV-TAT $_{48-57}$," refer to. Applicant have amended claim 9 to indicate that the term HIV-TAT $_{48-57}$ refers to SEQ ID NO:15. With regard to the terms FHV-coat $_{35-49}$ peptide, HTLV-II Rex $_{4-16}$ peptide, and BMV gag $_{7-25}$ peptide, Applicants respectfully submit that one of skill in the art would understand that:

FHV-coat$_{35-49}$ encodes a peptide of sequence RRRRNRTRRNRRRVR;

HTLV-II Rex$_{4-16}$ encodes a peptide of sequence TRRQRTRRARRNR; and

BMV gag$_{7-25}$ encodes a peptide of sequence KMTRAQRRAAARRNRWTAR.

The use of these types of arginine rich peptides (also known as cell penetrating peptides or Trojan peptides) for improving the cellular translocation of macromolecules was well known in the art at the time the instant application was filed. For example, Futaki *et al.* (J. Mol. Recognit. 2003 16:260-264) clearly describes all three peptides in Table 2, and reviews their ability to increase the efficiency of delivery of "proteins and other macromolecules" across membranes (Abstract). The Examiner will note that Table 2 refers to each of the three peptides using the same terms as used by Applicants in claim 9, and clearly identifies the sequences associated with each. Additionally, all three cell penetrating peptides are commercially available at Biosynthesis, Inc. (Lewisville, TX; http://www.biosyn.com/), and both FHV-coat$_{35-49}$ and HTLV-II Rex$_{4-16}$ are also sold by AnaSpec, Inc. (Freemont, CA; http://www.anaspec.com/). Applicants note that in all cases the peptides are referred to by the names FHV-coat $_{35-49}$ peptide, HTLV-II Rex $_{4-16}$ peptide, and BMV gag $_{7-25}$ peptide, respectively, as particularly claimed in the instant application. Applicants respectfully submit that one of skill in the art would unambiguously know what peptide sequences these terms referred to, and would further understand that the Applicants were in full possession of the four claimed peptides at the time the application was filed. Applicants respectfully request favorable reconsideration and withdrawal of the rejection.

The Examiner has rejected claim 12 as being indefinite for the recitation of the term "other platinum derivatives." Applicants have amended the claim to recite "other platinum compounds" as requested by the Examiner. Applicants respectfully request that this rejection be withdrawn.

The Examiner has rejected claims 23, 27, 28, 33-38, and 40-43 on the grounds that they lack a step, namely an effective amount used in the method. Applicants have amended the claims to refer to a "therapeutically effective amount" of the respective compound. Applicants believe that this amendment addresses the Examiner's concern, and respectfully request that this rejection be withdrawn.

Claims 1-3, 11, 12, 27, 28, and 33-39 are rejected under 35 U.S.C. § 102

The Examiner has rejected claims 1-3, 11, 12, 27, 28, and 33-39 under 35 U.S.C. § 102 on the grounds that they are anticipated by Yang *et al.*, as evidenced by Widmann *et al.* Applicants respectfully traverse the rejection.

The Examiner has stated that Yang *et al.* teaches the N-fragment (residues 1-455)

"enhances apoptosis of HeLa cells in the presence of cisplatin." Applicants respectfully submit that the Examiner has overstated the teachings of Yang *et al.*

Applicants submit that Yang et al. discloses an N2 fragment of RasGAP consisting of amino acids 158 to 455 that potentiates apoptosis and cell killing in genotoxin-treated tumor cells. However, in contrast to the Examiner's characterization, Yang et al. does not teach that the N2 fragment enhances apoptosis or the ability to selectively kill cancer cells, as particularly claimed in the instant invention. Selective killing of cancer cells cannot be deduced from Yang et al. because their experiments were conducted solely on HeLa cells.

As disclosed in the specification, a fundamental feature of Applicant's invention lies in the fact that an N2 sequence of RasGAP comprising the general amino acid sequence WxVVVTxxRTx enhances the ability of a genotoxin to selectively kill cancer cells. This is illustrated in particular in Example 2 and Figures 3, 4A, and 4B, which show that the TAT-RasGAP317-326 peptide, but not the control HIV-TAT48-57 peptide lacking the RasGAP sequences, enhanced the ability of cisplatin, adriamycin, and mitoxantrone to kill the tested cancer cell lines and did not, or only marginally did, induce apoptosis under control conditions. In contrast, the apoptotic response induced by cisplatin, adriamycin and mitoxantrone in the two non-cancer lines (HaCat and HUV-EC-C) was unaffected by the presence of the peptides.

Furthermore, Applicants note that the N-fragment of claim 1 (WxVVVTxxRTx) is neither noted nor commented upon in Yang et al.; consequently, this reference does not teach or suggest the claimed peptide WxVVVTxxRTx of the instant invention.

Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the above remarks, Applicants believe that the application is in condition for allowance. The Examiner is request to contact the undersigned for discussion of the above, if deemed appropriate. A Request for an Extension of Time is being filed herewith. The Commissioner is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. KZY-004US.

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Respectfully submitted,

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